

REMARKS/ARGUMENTS

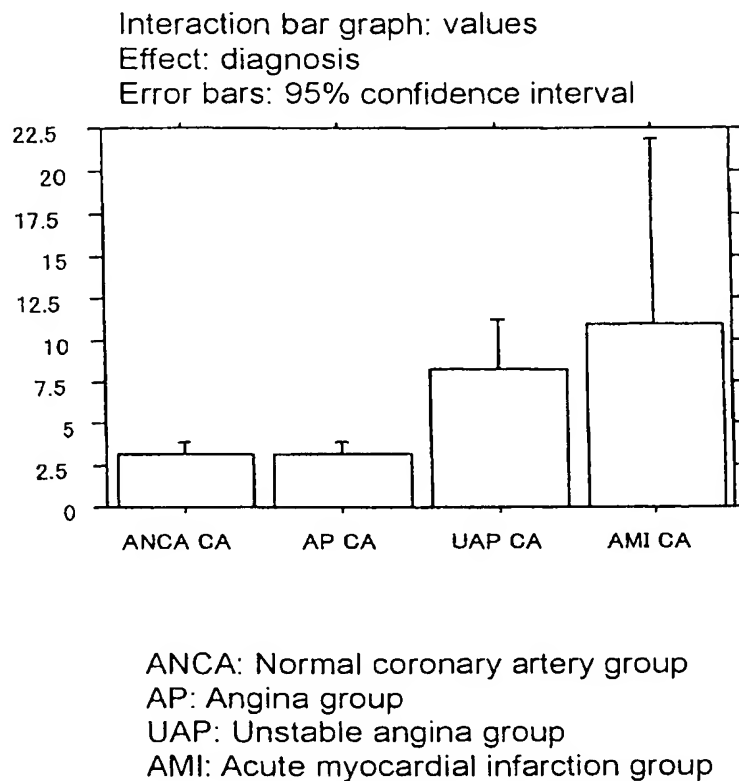
Claims 21-42 are pending. Claim 21 has been revised to refer to vascular injury associated with a coronary artery condition as described and exemplified on page 51 of the specification, see line 8 for the exact term. Vascular injury associated with coronary artery conditions were well characterized at the time of invention as shown herein, for example, by parameters such as those described at the bottom of page 8 and in the claims. Claim 21 also now provides antecedent basis for the source of the sample in the subject's blood, plasma or serum as disclosed on page 8, line 5 of the specification. Claims 37-40 find support on page 51 of the specification. Claims 41-42 find support in the sections bridging pages 3-4 and 4-5 and in the example on page 51 of the specification and in Fig. 4. No new matter has been introduced. Favorable consideration of this amendment and allowance of this case are respectfully requested.

Rejection—35 U.S.C. §112, first paragraph

Claims 21-36 were rejected under 35 U.S.C. 112, first paragraph, as not being enabled. Initially, the Examiner indicated enablement for a method for diagnosis of coronary artery condition (CA), unstable angina (UAP) and myocardial infarction (AMI) by measuring an increased level of PTX3 using an anti-PTX3 antibody in patients with the above conditions as compared to a defined control. Claim 21 requires comparison of the PTX3 level compared to a control value defined by a subject or subjects having normal coronary artery condition to determine a relative increase or decrease in PTX3 level with respect to the control, but not by an absolute numeric control value. What is being determined by the method is a relative increase or decrease with regard to the control, not by comparison to some absolute numeric value. The disclosure enables the determination of a relative increase or decrease in PTX3 level with respect to values found in subject(s) having normal coronary

artery conditions. There is no requirement that the comparison of claim 21 be by reference to a quantified, absolute numeric value in order for it to be enabled. Relative increases in PTX3 levels compared to values of subjects with normal coronary artery conditions, as well as subjects having increasing degrees of vascular injury are disclosed in the Examples (see page 51) and are depicted by Fig. 4, reproduced below.

Fig. 4



When an increase in PTX3 occurs with respect to subjects with normal coronary artery condition, then a greater extent of vascular injury is assessed.

The claimed method is based on a discovered nexus between an increase in PTX3 level and an increase in vascular injury as disclosed on page 5, lines 5-6 of the specification:

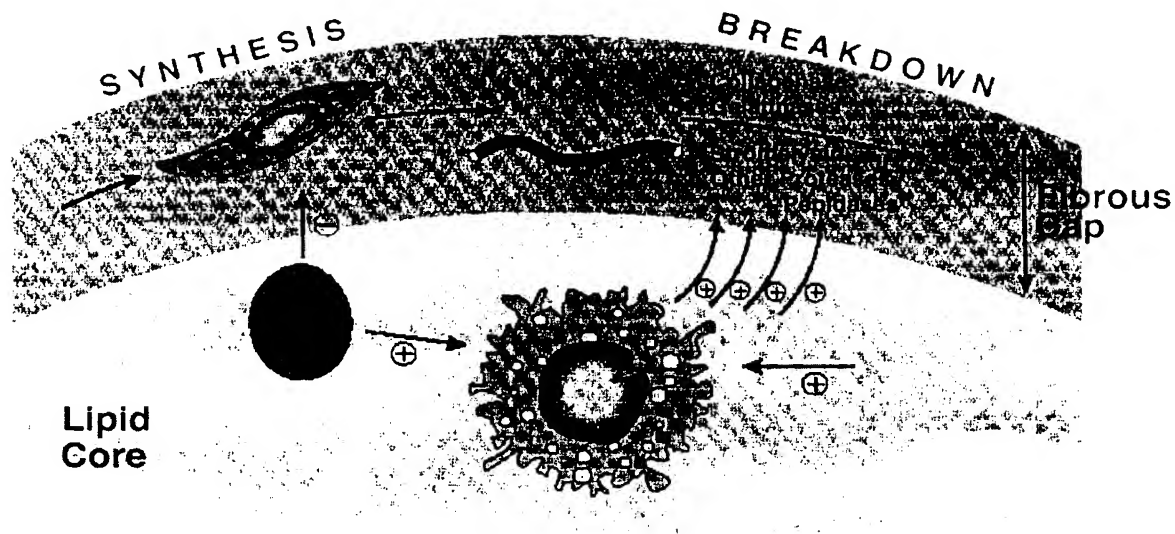
...the PTX3 level turned out to highly increase in parallel with the gravity of vascular injury.

The higher the level of PTX3, the more vascular injury. Once this nexus was discovered and disclosed by the inventors, those of skill in the art would have been able to practice the claimed method without undue experimentation since the determination of a relative increase or decrease in the PTX level in a sample (e.g., in samples obtained from the same patient over time) could have been easily be determined. As shown in Example 17 on page 52 of the specification, unlike increases observed for other markers, the relative increase in PTX3 does not correlate with inflammation, such as that caused by viral infection, but has been identified by the inventors “as a marker highly specific to the blood vessel”. This makes sense when understood in the context of the inventors’ discovery (see Example 16, page 51) that increases in PTX3 levels correlate with the extent or severity of vascular injury.

Vascular Injury. Histological assessment of vascular injury was well-known and convention in the art at the time of invention. There are no “undefined histological parameters” (OA, page 4, line 4) and the specification, paragraph bridging pages 8-9, provides a detailed description of what characterizes a vascular injury in claim 21: the extent of vascular injury is rated by “the following pathological histological parameters (a) lipid core size, (b) thickness of fibrous cap, (c) strength of shear stress, and (d) extent of inflammatory infiltration. Plaques are more readily ruptured, as (a) increases, (b) is thinner, (c) increases, and (d) increases”.

The Examiner asserts that the Applicants have not shown a nexus between vascular injury as characterized by the above parameters and a relatively higher level of PTX3 (OA, bottom half of page 5) and says only a correlation between PTX3 level in the blood of patients suffering from CA, UAP and AMI has been shown to be higher compared to patients not having these conditions. However, the specification shows that PTX3 levels significantly and progressively increase in stable angina (AP), unstable angina (UAP), and myocardial infarction (AMI) above PTX3 values of subjects having normal coronary arteries.

It was well known¹ that subjects having AP, UAP and AMI progressively exhibit signs of vascular damage as characterized by the histological parameters (a) lipid core size, (b) thickness of fibrous cap, (c) strength of shear stress, and (d) extent of inflammatory infiltration as shown by Libby, J. Int. Med. 247: 349 “Changing concepts of atherogenesis” and Moreno, J. Stroke and Cerebrovascular Diseases 10: 2-9 “Pathophysiology of Plaque Disruption and Thrombosis in Acute Ischemic Syndromes”. Libby, Fig. 2 (below), page 354, depicts the lipid core and fibrous caps showing how cells which release inflammatory mediators breakdown collagen in the fibrous cap, weakening it, see also the text on page 354, col. 1.



Moreno, page 8, left col., lines 7-8 indicates “Certain features, such as large lipid cores, thin fibrous caps, and dense macrophage infiltration, enhance the vulnerability of plaques, predisposing them to rupture”. Moreover, these same general histological parameters characterize vascular injury in other conditions like obesity, smoking or diabetes. Accordingly, the disclosure shows a clear nexus between PTX3 levels in the blood and the degree of vascular injury which can be described by any of these criteria. While the OA

¹ A patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

mentions vascular damage associated with obesity, smoking, diabetes and other conditions, it provides no objective reasoning to doubt that a similar nexus between PTX3 levels in the blood and vascular injury associated with these other conditions. Consequently, this rejection cannot be sustained because the inventors have demonstrated that a relative increase in PTX3 levels correlates with a greater extent or severity of vascular injury and because the histological criteria for describing vascular injury were well known at the time of invention

Rejection—35 U.S.C. §112, first paragraph

Claims 21-36 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for:

(a) “a correlation between the diseases of CA, UAP and MCI, and other undefined vascular diseases” (OA, page 6, lines 12-14). This basis for rejection is moot in view of the revision of the claims above to refer to vascular injury associated with a coronary artery condition as both described, histologically characterized, and exemplified in the specification. The state of the art at the time of invention is described above by Libby and Moreno and shows that histological characterization of coronary artery injuries was well-known.

A patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), see MPEP. The specification clearly characterizes what a vascular injury associated with a coronary artery condition is in the paragraph bridging pages 8-9 and shows that vascular injury progresses from patients having normal coronary artery condition, to those having angina, to those with unstable angina, and then to those with myocardial infarction. The bottom of page 8 of the specification specifically describes how each of these parameters correlate with the risk of plaque rupture. The specification also describes a correlation between these progressive vascular injuries and PTX3 levels, see e.g., Fig. 4. In

view of the above disclosure, the Applicants clearly were in possession of the claimed invention as of their filing date.

(b) “a defined control value” (OA, page 6, lines 14-15). This issue has been discussed above in relation to enablement. The Examiner has not said exactly what he considers a defined control value, but as discussed above, it is not necessary to specify a particular numerical value or numeric range to enable the invention. Page 7, [0014] of the specification specifically discloses that PTX3 levels may be determined quantitatively or by non-quantitative measurement. The concept of a controlled comparison to determine a relative increase with regard to normal subjects (e.g., subjects having normal coronary artery condition) was well-known at the time of invention. The invention requires determination of an increase in PTX3 level relative to subjects with normal coronary artery condition to assess a greater or progressing degree of vascular injury. This is exemplified in the specification (see page 51) and by Fig. 4 reproduced above.

(c) a “specific correlation between the recited histological parameters or the recited control value and the levels of PTX3” (OA, page 6, lines 15-16). The histological parameters in claim 21 are descriptive of vascular injury in coronary artery conditions. This is expressly described at the bottom of page 8 of the specification. Those of skill in the art would have recognized these histological parameters as useful for characterizing increasing vascular injury in coronary artery conditions as shown by Libby and Moreno. However, the invention is directed to determining a degree of vascular injury in a coronary artery condition by measuring PTX3 levels, not by comparison to these well-known descriptive histological parameters of vascular injury.

This rejection cannot be sustained because the specification clearly describes and exemplifies a correlation between PTX3 levels and the degree of vascular injury and because the histological parameters used to more precisely describe the type of vascular injury are

expressly described on pages 8-9 of the specification and were well-known in the art. For all these reasons as well as those given in their prior response, the Applicants were in possession of the claimed subject matter on the date of the invention and this lack of description rejection cannot be sustained.

Provisional Rejection--Obviousness-type Double Patenting

Claims 21-36 were rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-5 of copending U.S. Application 12/092,272. This rejection is moot in view of the cancellation of these claims. Moreover, should it be applied to the new claims, the foregoing amendments and remarks address all the remaining rejections and place this application in condition for allowance. Accordingly, this provisional double patenting rejection can be withdrawn since the copending application has not yet been allowed, MPEP 804(I)(B).

Rejection—35 U.S.C. §112, second paragraph

Claims 21-29 and 31-36 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for using the phrase “in the blood”. This rejection is moot in view of the amendments above.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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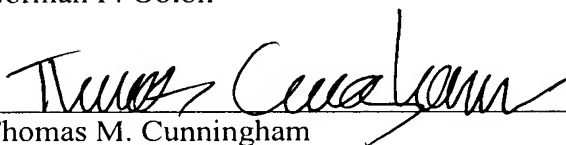
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